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RESEARCH SUBMISSIONS

Vessel-wall MRI in primary headaches: The role of neurogenic inflammation

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Abstract

Objective: The purpose of this study was to investigate if vessel-wall magnetic resonance imaging (VW-MRI) could differentiate among primary headaches disorders, such as migraine and cluster headache (CH), and detect the presence of neurogenic inflammation.

Background: The pathophysiology of primary headaches disorders is complex and not completely clarified. The activation of nociceptive trigeminal afferents through the release of vasoactive neuropeptides, termed "neurogenic inflammation," has been hypothesized. VW-MRI can identify vessel wall changes, reflecting the inflammatory remodeling of the vessel walls despite different etiologies.

Methods: In this case series, we enrolled seven patients with migraine and eight patients with CH. They underwent a VW-MRI study before and after the intravenous administration of contrast medium, during and outside a migraine attack or cluster period. Two expert neuroradiologists analyzed the magnetic resonance imaging (MRI) studies to identify the presence of vessel wall enhancement or other vascular abnormalities.

Results: Fourteen out of 15 patients had no enhancement. One out of 15, with migraine, showed a focal parietal enhancement in the intracranial portion of a vertebral artery, unmodified during and outside the attack, thus attributable to atherosclerosis. No contrast enhancement attributable to neurogenic inflammation was observed in VW-MRI, both during and outside the attack/cluster in all patients. Moreover, MRI angiography registered slight diffuse vasoconstriction in one of seven patients with migraine during the attack and in one of eight patients with cluster headache during the cluster period; both patients had taken triptans as symptomatic therapy for pain.

Conclusions: These preliminary results suggest that VW-MRI studies are negative in patients with primary headache disorders even during migraine attacks or cluster

Abbreviations: CH, cluster headache; ICA, internal carotid artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TGVS, trigeminovascular system; TOF, time of flight; VW-MRI, vessel-wall magnetic resonance imaging.

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periods. The VW-MRI studies did not detect signs of neurogenic inflammation in the intracranial intradural vessels of patients with migraine or CH.

KEYWORDS
cluster headache, migraine, primary headaches, secondary headaches, vessel-wall magnetic resonance imaging

INTRODUCTION

Distinguishing between primary and secondary headaches is mandatory because of its therapeutic and prognostic implications. By definition, primary headaches disorders are not the result of any other underlying disease or process, unlike secondary ones in which the headache occurs in close temporal relation to another disorder that is known to cause headache.[1]

Characterizing and diagnosing different headache disorders is frequently tricky if based only on clinical and routine measurements, but neuroimaging could help in distinguishing between primary and secondary headaches.[2,3]

Although the pathophysiology of primary headache diseases is complex, the activation of trigeminal afferents innervating pial, arachnoid, and dural blood vessels (the trigeminovascular system [TGVS]) has been suggested.[1,4,5] This phenomenon has been termed "neurogenic inflammation" to highlight the similarity to the inflammation process, because of its effects of meningeal blood vessel dilation, plasma extravasation, and platelet activation.[1,5]

Among different neuroradiological techniques, vessel-wall magnetic resonance imaging (VW-MRI) has emerged as a promising magnetic resonance imaging (MRI) sequence that allows detecting wall changes and reflects the inflammatory remodeling of the vessel walls despite different etiologies.[6–9] In fact, in a substantial proportion of secondary headaches, such as sentinel headache in case of aneurysm rupture or in case of reversible cerebral vasoconstriction syndrome or vasculitis, an inflammatory process in the vessel wall has been demonstrated to be responsible for the symptoms[10] and VW-MRI has been proposed as a useful tool to assess the causes.[8,10–12]

As in primary headaches disorders the pain is sustained by neurogenic inflammation, we wondered if VW-MRI could differentiate between different primary headaches and if a specific enhancement pattern is present as for secondary headaches. Moreover, we wondered if the neurogenic inflammation theory of migraine or cluster headache (CH) could finally be supported by the only currently available technique capable of visualizing the remodeling inside vessel walls.

MATERIALS AND METHODS

We screened patients with clinical diagnosis of migraine (with or without aura) or episodic CH, following the International Classification of Headache Disorders, 3rd edition, presenting to the Headache Centre of IRCCS Istituto delle Scienze Neurologiche di Bologna.[13] Other inclusion criteria were the absence of contraindication to perform a contrast enhanced MRI and the signing of an informed consent document. We included patients who consecutively agreed to perform a double MRI study and for whom the Neuroradiology Service was able to perform the examinations in the specific times as per study protocol. Therefore, the study design consists of a case series, with a preplanned analysis.

Patients' clinical history was traced in a face-to-face semistructured interview, concerning headache characteristics (type, location, side of pain, associated autonomic symptoms, duration, responsiveness to analgesic therapies, triggers, and ongoing medications), lifestyle (smoke and use of alcohol or drugs), and comorbidities (rheumatologic disease, hypertension, diabetes, and known atherosclerotic plaques).

Patients underwent brain MRI with VW sequences before and after the administration of contrast agent and magnetic resonance angiography (MRA), both during and outside a migraine attack or cluster period. For patients with migraine, the MRI study during the attack was performed within 24 h from the onset of pain, whereas for patients with CHs, the MRI study was performed during the cluster period.

Two expert neuroradiologists (authors L.L.G. and L.C.) with more than 5 and 15 years of experience independently evaluated all the MRI studies and reported the presence of intracranial vessels' alterations, such as stenosis, malformations or vessel wall enhancement, evaluating coronal, axial and sagittal maximal production rate reconstructions for both VW and time of flight (TOF) sequences. In particular, intracranial intradural arteries were evaluated both pre and post-contrast agent administration in VW-MRI sequences, with particular attention to vessel wall thickness, signal intensity, and contrast enhancement. Moreover, on 3D TOF MRA, the bilateral diameter of each internal carotid artery (ICA; in the supraclinoid portion), of the intracranial portion of the vertebral arteries (the V4 segments), of the middle portion of the basilar artery, of the anterior cerebral artery (particularly in the A1 segments), of the middle cerebral artery (particularly in the M1 segments), and of the posterior cerebral artery (particularly in the P1 segments) were evaluated by both neuroradiologists and the mean value was used to reduce measurement bias. Vasoconstriction or vasodilatation was reported if the vessel's diameter was reduced or augmented by more than 20% on the MRI studies. All evaluations were performed blind to diagnosis and the time of acquisition as the MRIs were re-evaluated subsequently. Due to the small number of cases, an interobserver

agreement between the two neuroradiologists was not possible and, thus, when a concordance was not possible, the evaluation of the more experienced neuroradiologist was used. This is the primary analysis of these data and no previously published manuscript contains data used in this study.

MRI protocol

Patients were scanned on the same 3T scanner (MagnetomSkyra; Siemens Healthcare, Erlangen, Germany). A three-dimensional (3D) High-Resolution Vessel Wall MRI (field of view 160 mm, time echo 38 ms, time repetition 1000 ms and anisotropic voxels of $0.3 \times 0.3 \times 0.6$ mm) was performed before and after the administration of 0.1 mmol/kg of gadolinium contrast agent (ProHance; Bracco, Milano, Italy), as previously described.[12] The VW-MRI protocol also included 3D T1-w, fluid attenuation inversion recovery T2-w, susceptibility weighted imaging and TOF (with maximum intensity projection reconstructions), and two-dimensional (2D) axial T2-w and diffusion weighted imaging sequences.

Standard protocol approvals and patient consents

The study was approved by the Local Ethics Committee of the health service of Bologna (Comitato Etico Indipendente Area Vasta Emilia Centro: CE17179) and all patients gave their written informed consent to study participation.

Statistical analyses

The analysis was conducted for descriptive purpose (sample of patients, type of headache, demographic characteristics, ongoing therapies, and MRI aspects). We reported descriptive statistics using frequency counts and percentages (sex, ongoing therapies, and MRI aspects), as well as mean (age). We used Excel software to calculate these values.

RESULTS

We examined seven patients with migraine and eight patients with episodic CH. Clinical and demographic characteristics are reported in Table 1 for patients with migraine and in Table 2 for patients with cluster. In the patients with migraine, six patients (85.7%) were women and mean age was 42.9 years. Six were on preventive therapy: three with amitriptyline, one with amitriptyline plus atenolol, one with gabapentin, and one with topiramate. In the CH group, seven of eight patients (87.5%) were men and the mean age was 43.9 years. Five of them took an oral preventive therapy (4 verapamil and 1 lithium), whereas three of them were treated with greater occipital nerve local steroid injections.

TABLE 1 Clinical features of patients with migraine

Migraine clinical features																		
Patient	Diagnosis	Age (y)	Sex	Laterality of pain	Pulsatility of pain	Photo-/phonophobia	Frequency (medium no. attacks/month)	Duration (h)	Ongoing preventive therapy	Attack therapy	Hypertension	Diabetes	Dyslipidemia	Rheumatologic illness	Carotid US	Coffee	Smoke	Alcohol
#1	M. without aura	68	F	Left or right	Yes	Yes	3	72	Amitryptiline	Eletriptan	Yes	No	Yes	No	Yes	No	No	No
#2	M. without aura	46	F	Bilateral	Yes	No	10	24	Gabapentin	Eletriptan	No	No	No	No	No	No	No	No
#3	M. without aura	28	F	Right	No	Yes	8	24	Escitalopram	Zolmitriptan	No	No	No	No	No	No	No	No
#4	M. without aura	29	F	Left or right	Yes	No	3	12	Topiramate	Sumatriptan plus ibuprofen	No	No	No	No	No	No	No	No
#5	M. without aura	46	M	Left	No	No	10	4	Amitriptyline	Paracetamol	Yes	No	No	No	No	No	No	No
#6	M. with aura	33	F	Left or right	Yes	Yes	10	24	Amitriptyline	Ibuprofen	No	No	No	No	No	No	No	No
#7	M. with aura	50	F	Bilateral	Yes	Yes	9	24	Amitriptyline, atenolol	Rizatriptan	No	No	No	No	No	Yes	No	No

TABLE 2 Clinical features of patients with cluster headache

Cluster headache clinical features																			
Pat.	Age (y)	Sex	Laterality of pain	Stabbing pain	Tearing	Rhinorrhea	Conjunctival injection	Ptosis	Duration (min)	Ongoing preventive therapy	Attack therapy	Hypertension	Diabetes	Dyslipidemia	Rheumatologic illness	Carotid US	Coffee	Smoke	Alcohol
#1	38	M	Right	Yes	Yes	Yes	No	No	50′	Verapamil	Rizatriptan	No	No	No	No	No	No	No	Yes
#2	44	M	Left	No	Yes	No	No	No	60′	Valproate	Sumatriptan	No	Yes	Yes	No	No	No	No	No
#3	58	M	Left	Yes	Yes	Yes	Yes	No	60′	Verapamil	Sumatriptan	Yes	No	No	No	No	No	Yes	No
#4	48	M	Left	Yes	Yes	Yes	Yes	No	180′	GON injections	Sumatriptan	No	No	No	No	No	No	No	No
#5	40	M	Left	Yes	Yes	Yes	Yes	Yes	40′	GON injections	Sumatriptan	No	No	No	No	No	No	No	No
#6	42	F	Left	Yes	Yes	Yes	Yes	No	120′	Verapamil	Sumatriptan	No	No	No	No	No	No	No	Yes
#7	32	M	Right	Yes	Yes	Yes	No	Yes	240′	GON injections	Sumatriptan	No	No	No	No	No	No	Yes	No
#8	49	M	Left	Yes	Yes	No	Yes	Yes	180′	Lithium	Sumatriptan	No	No	No	No	No	No	Yes	No

One patient with CH did not undergo the examination outside the cluster period because of restrictions due to the coronavirus disease 2019 (COVID-19) pandemic, whereas three patients with migraine reported adverse events during the examination, such as nausea and vomiting, and did not repeat the examination outside the attack.

Neuroradiological features are shown in Table 3 for patients with migraine and in Table 4 for patients with cluster. One 46-year-old female patient with migraine with no vascular risk factors presented a focal linear parietal enhancement after intravenous contrast administration in the left intracranial vertebral artery, unmodified during and outside the migraine attack, and thus possibly attributable to an initial atheromatous plaque (Figure 1). No other vessel wall enhancement was reported in the other patients, both during and outside the migraine or cluster attack.

Slight diffuse vasoconstriction was registered in one female patient with migraine and in one male patient with cluster on the MRI performed during the attack. In both cases, such vasoconstriction was not confirmed on the MRI performed outside the attack and both patients had taken sumatriptan for pain.

DISCUSSION

In our study, neurogenic inflammation was not detected by VW-MRI in the intracranial intradural vessels of patients with migraine and patients with CH.

It is known that primary headaches have a complex pathophysiology, although their exact mechanisms are still unclear. Concerning migraine, the pain is thought to be caused by the activation of the TGVS, which consists of nociceptive trigeminal afferents surrounding the different types of intracranial meningeal blood vessels.[1] The TGVS afferents transmit the nociceptive stimuli to the brainstem[14,15] and then to the hypothalamus and ventro-postero-medial, posterior, and intralaminar thalamus,[14,16] passing through the trigeminal ganglion. Moreover, the activation of the TGVS leads to the perivascular release of proinflammatory neuropeptides, necessary for the maintenance of activation and sensitization of the afferents.[1,5] The release of these neuropeptides results in meningeal blood vessel dilation, plasma extravasation, and platelet activation, a phenomenon[1,5] that shares some similarities with the inflammation process.

In CH, the involvement of the TGVS component has also been demonstrated,[17–19] although pain stands both on a peripheral (TGVS component)[17–19] and on a central (hypothalamic) component.[20] Therefore, even if the brain areas involved in the central pain network for CH are different from those involved in migraine,[21,22] the TGVS component is the same and supposed to be based upon the calcitonin gene-related peptide release.[18,23] In fact, calcitonin gene-related peptide is the target of new treatments for migraine and, although with lower effectiveness, for CH.[24]

It is commonly accepted that neuroinflammation is a localized form of inflammation occurring in both the peripheral nervous system and central nervous system[25,26] in particular conditions, such as

TABLE 3 Neuroradiological features of patients with migraine

	MRI–out			MRI–in		
	MRA			MRA		
Pat.	Stenosis	Malformations	HR-VW MRI	Stenosis	Malformations	HR-VW MRI
#1	No	No	Negative	No	No	Negative
#2	No	No	Left V4 and internal carotid focal parietal enhancement[b]	No	No	Left V4 and internal carotid focal parietal enhancement[b]
#3				No	No	Negative
#4	No	No	Negative	Yes[a]	No	Negative
#5				No	No	Negative
#6				No	No	Negative
#7	No	No	Negative	No	No	Negative

Abbreviations: HR-VW, high-resolution vessel wall; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.
[a]Diffuse intracranial vasoconstriction.
[b]See Figure 1.

TABLE 4 Neuroradiological features of patients with cluster headache

	MRI–out			MRI–in		
	MRA			MRA		
Pat.	Stenosis	Malformations	HR-VW MRI	Stenosis	Malformations	HR-VW MRI
#1	No	No	Negative	No	No	Negative
#2	No	No	Negative	No	No	Negative
#3	No	No	Negative	No	No	Negative
#4	No	No	Negative	No	No	Negative
#5	No	No	Negative	No	No	Negative
#6	No	No	Negative	No	No	Negative
#7				No	No	Negative
#8	No	No	Negative	Yes[a]	No	Negative

Abbreviations: HR-VW, high-resolution vessel wall; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.
[a]Diffuse intracranial vasoconstriction.

primary headaches. Therefore, we wondered if novel and advanced neuroimaging MRI techniques could permit us to identify it in these types of primary neurovascular headaches.

In fact, to distinguish among primary and secondary headaches, but also between different types of secondary headaches, neuroimaging plays a crucial role, as in most secondary headaches, an attributable cause could be identified.[2,27] Among different neuroradiological techniques, a specific MRI sequence named vessel-wall has emerged because of its ability to detect wall changes inside intracranial vessels, being demonstrated to reflect the remodeling inside the vessel wall independently of the etiologies.[6,11] Currently, VW-MRI sequences are extensively used in clinical practice to distinguish between different causes of cerebrovascular diseases, thanks to their specific wall enhancement and MRA features. In fact, the use of VW-MRI in conjunction with MRA has been demonstrated to be able to distinguish between different etiologies, as, for example, the instability of intracranial aneurysmal wall,[6,8,9,28,29] reversible cerebral vasoconstriction syndrome,[30,31] dissections, atheromatous plaques, and inflammatory/infectious diseases.[7,8,11,32,33]

As VW-MRI has been demonstrated to be a useful tool in the differential diagnosis between secondary headaches, we wondered if it can also distinguish between primary headaches. As stated, in primary headaches, neurogenic inflammation through the TGVS component is argued and thus we wondered if this neurogenic inflammation extends to the intracranial arteries, and particularly to the proximal intracranial vessels. We specifically observed the intracranial portion of the ICA as it is innervated by the ophthalmic division of the trigeminal nerve, which is supposed to be part of the TGVS.[34,35]

Thus, we performed VW-MRI sequences in patients with migraine and CH, both during and outside pain, to evaluate if a particular pattern of enhancement is present. In our study, we find only a single focal parietal enhancement in one patient with migraine, unmodified outside and during the attack, thus attributable to atherosclerosis (see

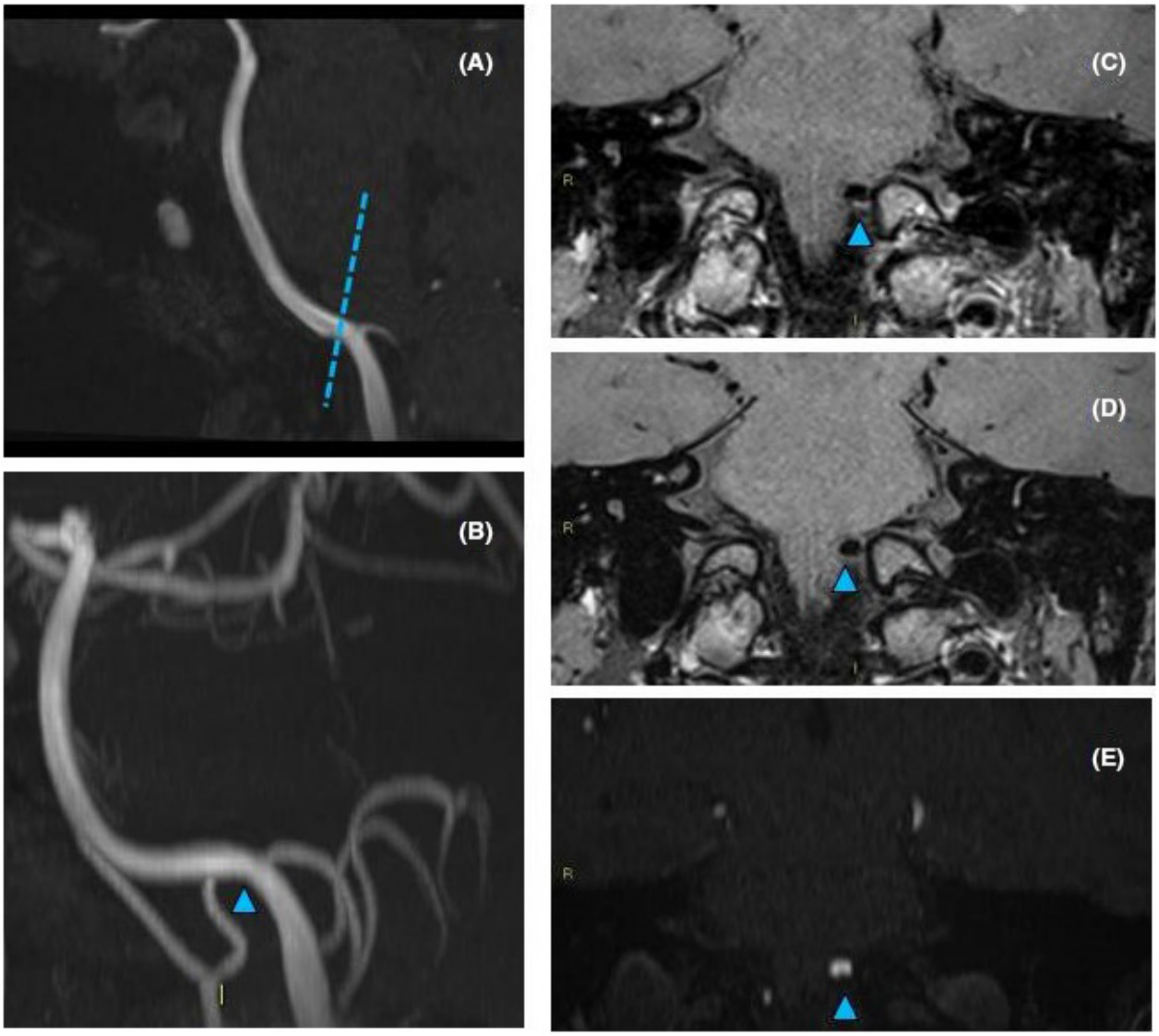

FIGURE 1 Neuroradiological findings of migraine patient #2, focused on left vertebral artery. (A) Sagittal reconstruction of 3D time of flight (TOF) sequence of the intracranial left vertebral artery with blue dotted line across the emergency of the postero-inferior cerebellar artery (PICA), representing the plane of section of panels C, D, and E. (B) Maximum intensity projection sagittal oblique reconstruction of the same TOF sequence (thick slices of 10 mm) where the blue arrowhead shows the presence of a mild stenosis at the emergence of the PICA. High resolution vessel wall magnetic resonance imaging with (C) and without (D) contrast medium in a transverse section passing through the dotted line of image A, showing the presence of a mild contrast enhancement at this level (blue arrowheads). (E) Maximal production rate coronal reconstruction of the same 3D TOF sequence showing the presence of a mild notch in the inferior portion of the vertebral artery lumen (blue arrowhead), at the level of the emergence of the PICA (blue dotted line in A)

Figure 1). In no other patient did the VW-MRI show peculiar enhancement or thickness, either during or outside the attack.

The lack of wall enhancement in primary headaches did not rule out the neurogenic inflammation theory through the TGVS component. In fact, VW-MRI has known pitfalls that must be taken into account. It is known that the visualization of contrast enhancement in the cavernous segment of the ICA is difficult due to the fact that it runs inside the cavernous sinus, which shows diffuse enhancement after contrast agent administration.[36] The cavernous segment of the ICA is the most richly innervated part by the trigeminal fibers, in which the TGVS component is considered to be present. Thus, a limitation of this study is the difficulty to correctly assess the presence of enhancement of the cavernous segment of the ICA with current available VW-MRI sequences.

Despite the impossibility to detect vessel wall enhancement with the currently available VW-MRI technique, our study demonstrated the lack of enhancement in the intradural intracranial vessels. Therefore, we can assess that neurogenic inflammation in primary headaches did not extend to the vessel of the circle of Willis and beyond. In fact, VW-MRI has been demonstrated capable to highlight the presence of blood–brain barrier disruption.[37] Thus, the neurogenic inflammation may be localized in the cavernous portion of the ICA, innervated by the trigeminal fibers, where the TGVS component is present.

In this study, we additionally report the presence of slight diffuse vasoconstriction, seen in two patients (one with migraine and one with cluster) during the attack, both recovered on the MRI performed outside the attack. Both patients had taken sumatriptan for pain, but these findings could not be explained as data in literature are not conclusive concerning intracranial angiographic modifications during migraine or cluster attacks,[38–40] and for triptans' effect on intracerebral vessels' circumference modifications.[41] Considering that our study was focused on VW-MRI features and the slight diffuse vasoconstriction was seen only in two patients, we do not have enough data to give a fair interpretation of this last finding. As a limitation, three patients with migraine did not perform the outside-pain examination due to adverse events during the examination. These side effects could be attributable both to the autonomic symptoms associated with the migraine attack and to the injection of contrast medium.

Further studies with larger sample sizes are required to confirm the findings of this preliminary study.

CONCLUSIONS

In this study, VW-MRI sequences are used to evaluate patients with primary headaches, both during and outside pain. Although it presents many limitations, such as the small number of patients and the absence of an MRI study both during and outside pain for all patients, the lack of wall enhancement in the VW-MRI sequences in the intracranial intradural vessels rules out the presence of blood–brain barrier disruption or vessel wall remodeling due to the neurogenic inflammation in primary headaches. Due to the current limitations of VW-MRI in the visualization of the cavernous sinus, future research and improvements are needed to assess whether VW-MRI will be able to differentiate among different primary headaches on the basis of their mechanism of neurogenic inflammation.

Moreover, these data may support VW-MRI negative predictive factor for secondary headaches and suggest its use in confirming the presence of secondary causes of headache in positive cases.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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